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REMARKS

The Amendment

The Amendment in the specification clarifies the relationship of the priority applications.

New Claim 12 is supported by page 1, line 21; page 7, line 19; page 15, line 10; and page 38, line 6.

New Claim 13 is supported by page 29, lines 15-19.

No new matter is added in any of the above amendments. The Examiner is respectfully requested to enter the amendment.

Respectfully submitted,

Date: July 19, 2004

Viola T. Kung (Reg. No. 41,131)

HOWREY SIMON ARNOLD & WHITE, LLP
301 Ravenswood Avenue
Box No. 34
Menlo Park, CA 94025
Ph. (650) 463-8181
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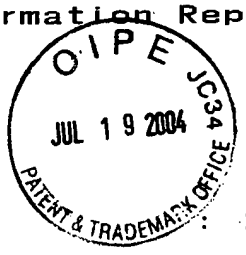

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CITY/STATE: Washington, D.C.

FAX NO: (703) 746-5125 Phone No.: (703) 306-4538

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NAME: Albert P. Halluin/Viola T. Kung (Judy)

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Application Serial No.: 10/007,451
Filed: November 6, 2001

Viola T. Kung,
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Application Serial No.: 10/007,451
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Viola T. Kung,
Phone No.: (650) 463-8181

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Judy Paradoski

HOWREY SIMON ARNOLD & WHITE, LLP
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Menlo Park, CA 94025
(650) 463-8109

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FORM PTO-1083

Attorney Docket No. 03678.0022.CNUS02

In re application of William PENDERGAST, *et al.*
Appl. No. 10/007,451
Filed: November 6, 2001
For: **CERTAIN DINUCLEOTIDES AND THEIR USE AS MODULATORS OF MUCOCILIARY CLEARANCE AND CILIARY BEAT FREQUENCY**

THE COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith are the following:

1. PTO Form 1083 (1 pg.) (in duplicate);
2. Preliminary Amendment (9 pgs.);
3. Marked-Up Version Showing Changes Made to the Specification (3 pg.);
4. Marked-Up Version Showing Changes Made to the Claims (4 pg.);
5. Terminal Disclaimer over U.S. Patent No. 6,348,589 (1 pg.); and
6. Terminal Disclaimer over U.S. Patent No. 5,837,861 (1 pg.).

xx The U.S. Patent and Trademark Office is hereby authorized to charge the fee of **$220.00** for 2 terminal disclaimers submitted to Deposit Account No. 08-3038.

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Date: January 24, 2003

Albert P. Halluin (Reg. No. 25,227)
Viola T. Kung (Reg. No. 41,131)

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Judy Paradoski

HOWREY SIMON ARNOLD & WHITE, LLP
301 Ravenswood Avenue
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Menlo Park, CA 94025
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FORM PTO-1083

Attorney Docket No. 03678.0022.CNUS02

In re application of William PENDERGAST, *et al.*
Appl. No. 10/007,451
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THE COMMISSIONER FOR PATENTS
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Judy Paradoski

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

William PENDERGAST, *et al.*

Application Serial No.: 10/007,451

Filed: November 6, 2001

For: CERTAIN DINUCLEOTIDES AND THEIR USE AS MODULATORS OF MUCOCILIARY CLEARANCE AND CILIARY BEAT FREQUENCY

Group Art Unit: 1623

Examiner: Owens, Howard

Attorney's Docket No: 03678.0022.CNUS02

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

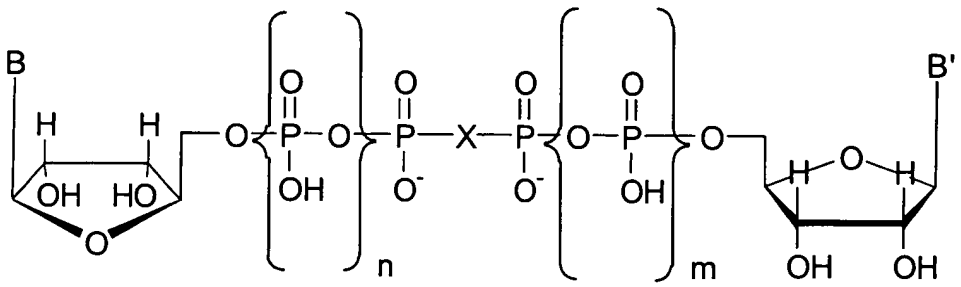
Applicant submits herewith a Preliminary Amendment. The Examiner is respectfully requested to enter the amendment prior to considering the application.

THE AMENDMENT

In the Specification

Replace the paragraph at page 11, lines 5-7, with the following paragraph:

Formula IB



Replace the paragraph starting at page 12, line 15, with the following paragraph:

Thus the substituted derivatives of adenine include adenine 1-oxide; 1,N^6-(4- or 5-substituted etheno) adenine; 6-substituted adenine; or 8-substituted aminoadenine, where R' of the 6- or 8-HNR' groups are chosen from among: arylalkyl (C_{1-6}) groups with the aryl moiety optionally functionalized as described below; alkyl; and alkyl groups with functional groups therein, such as: ([6-aminohexyl]carbamoylmethyl)-, and ω-acylated- amino(hydroxy, thiol and carboxy)alkyl(C_{2-10})- and their ω-acylated-amino (hydroxy, thiol and carboxy) derivatives where the acyl group is chosen from among, but not limited to, acetyl, trifluoroacetyl, benzoyl, substituted-benzoyl, etc., or the carboxylic moiety is present as its ester or amide derivative, for example, the ethyl or methyl ester or its methyl, ethyl or benzamido derivative. The ω-amino(hydroxy, thiol) moiety may be alkylated with a C_{1-4} alkyl group.

Replace the paragraph starting at page 14, line 22, with the following paragraph.

The compounds of the present invention encompass their pharmaceutically acceptable esters, such as, but not limited to, acetyl and benzoyl esters. The esters may be made by reaction of the desired hydroxy compound with the appropriate acid, activated with carbonyldiimidazole, dicyclohexylcarbodiimide or other suitable condensing agent, or with an acid anhydride or acid chloride with or without a basic catalyst such as a tertary amine, quaternary ammonium salt or an inorganic base.

Replace the paragraph starting at page 17, line 1, with the following paragraph:

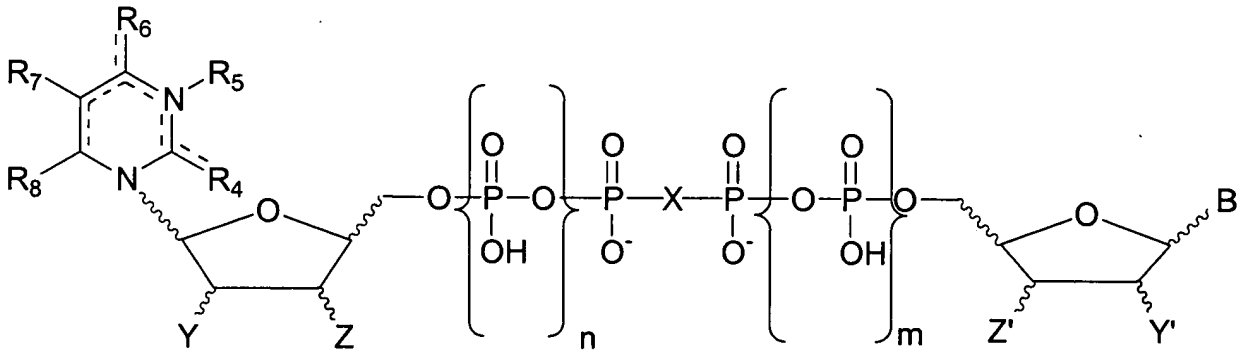
Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example: sodium carboxymethylcellulose, methylcellulose and sodium alginate. Dispersing or wetting agents may be a naturally-occurring phosphatide or condensation products of an allylene oxide with fatty acids, or condensation products of ethylene oxide with long chain aliphatic alcohols, or condensation products of ethylene oxide with partial esters from fatty acids and a hexitol, or condensation products of ethylene oxide with partial esters derived from fatty acids

and hexitol anhydrides. Those skilled in the art will recognize the many specific excipients and wetting agents encompassed by the general description above. The aqueous suspensions may also contain one or more preservatives, for example, ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

In the Claims

1. (Amended) A compound of Formula IIIA:

Formula IIIA



wherein:

X is oxygen, methylene, difluoromethylene, imido;

n = 0, 1, or 2;

m = 0, 1, or 2;

n + m= 0, 1, 2, 3, or 4;

B is a purine or a pyrimidine residue linked through the 9- or 1-position, respectively;

Z = OH or N_3;

Z' = OH or N_3;

Y = H or OH;

Y' = H or OH;

provided that when Z is N_3, Y is H or when Z' is N_3, Y' is H;

R_4 is hydroxy, amino, cyano, aralkoxy, C_{1-6} alkoxy, C_{1-6} alkylamino, or dialkylamino;

R_5 is hydrogen, acyl, C_{1-6} alkyl, phenyloxy, C_{1-5} alkanoyl or absent;

R_6 is oxo, hydroxy, mercapto, C_{1-4}alkoxy, C_{7-12}arylalkoxy, C_{1-6}alkylthio, amino, C_{1-5} disubstituted amino, triazolyl, C_{1-6}alkylamino or di-C_{1-4}alkylamino, where the alkyl groups is optionally linked to form a heterocycle or link to N^3 to form a substituted ring; or

R_5 and R_6 taken together form a 5-membered fused imidazole ring between positions 3 and 4 of the pyrimidine ring, which is optionally substituted on the 4- or 5- positions of the etheno moiety with C_{1-4}alkyl, phenyl, or phenyloxy, which themselves are optionally substituted;

R_7 is hydrogen, hydroxy, cyano, nitro, substituted and unsubstituted C_{2-8}alkenyl, phenyl, substituted and unsubstituted C_{2-8}alkynyl, halogen, CF_3, substituted and unsubstituted C_{1-6}alkyl, allylamino, bromovinyl, ethyl propenoate, propenoic acid; or

R_6 and R_7 taken together form a 5 or 6-membered saturated or unsaturated ring bonded through N or O at R_6, such ring optionally contain substituents that themselves contain functionalities;

R_8 is hydrogen, amino or di-C_{1-4}alkylamino, C_{1-4}alkoxy, C_{7-12}arylalkoxy, C_{1-4}alkylthio, C_{7-12}arylalkylthio,carboxamidomethyl, carboxymethyl, methoxy, methylthio, phenoxy or phenylthio; provided that when R_8 is amino or substituted amino, R_7 is hydrogen;

provided that when B = adenine, adenine 1-oxide, or $1,N^6$-ethenoadenine, then:

(a) $R_6 \neq$ oxo when R_4 = oxo, Y = Z = OH and $R_5 = R_7 = R_8$ = H;

(b) $R_7 \neq$ Br when $R_4 = R_6$ = oxo, Y = Z = OH, and $R_5 = R_8$ = H;

provided that when B = adenine, then:

(a) $R_6 \neq$ amino when R_4 = oxo, Y = Z = OH, R_5 is absent, $R_7 = R_8$ = H, and n + m = 0, 1, or 2;

(b) $R_7 \neq CH_3$ when $R_4 = R_6$ = oxo, Y = H, Z = OH, and $R_5 = R_8$ = H;

(c) $R_7 \neq$ F when $R_4 = R_6$ = oxo, Y = H, Z = OH, $R_5 = R_8$ = H and n + m = 2;

provided that when B = thymine, Y'= H and Z' = N_3; then $R_7 \neq F$, when $R_4 = R_6$ = oxo, Y = OH, Z = OH, $R_5 = R_8$ = H, and n + m =0;

provided that when B = thymine, Y' = H and Z' = N_3; then $R_7 \neq CH_3$ when $R_4 = R_6$ = oxo, Y = H, Z = N_3, $R_5 = R_8$ = H, and n + m =0;

provided that when B = guanine, then:

(a) $R_6 \neq$ oxo when R_4 = oxo, Y = Z = OH, $R_5 = R_7 = R_8$ = H and n + m =1 or 2;

(b) $R_6 \neq$ amino when R_4 = oxo, Y = Z = OH, R_5 is absent, $R_7 = R_8$ = H, n+m=1 or 2;

provided that when B is uridine, or 5-Br-uridine, then

(a) $R_6 \neq$ oxo when R_4 = oxo, Y = Z = OH and $R_6 = R_7 = R_8$ = H;

(b) $R_7 \neq$ Br when $R_4 = R_6$ = oxo, Y = Z = OH, and $R_5 = R_8$ = H;

provided that when B is 5-FU, then $R_7 \neq F$, when $R_4 = R_6$ = oxo, Y = H, Z = OH, $R_5 = R_8$ = H, and n + m= 0;

provided that when B is cytosine, then $R_6 \neq$ amino, when R_4 = oxo, Y = Z = OH, R_5 is absent, $R_7 = R_8$ = H, and n + m = 1, or 2; and

provided that when B is cytosine, then $R_6 \neq$ oxo, when R_4 = oxo, Y = Z = OH and $R_6 = R_7 = R_8$ = H, and n + m =2.

5. (Amended) A pharmaceutical composition comprising a compound of Formula IIIA or IIA as described in Claim 1 or 2, or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier therefor.

6. (Amended) A method of treating chronic obstructive pulmonary diseases in a mammal by administering an effective chronic obstructive pulmonary disease treatment amount of a compound of Formula IIIA or IIA as described in Claim 1 or 2.

7. (Amended) A method of treating sinusitis, otitis media or nasolacrimal duct obstruction in a mammal by administering an effective mucus secretion clearing amount of a compound of Formula IIIA or IIA as described in Claim 1 or 2.

8. (Amended) A method of treating dry eye in a mammal by administering an effective dry eye treatment amount of a compound of Formula III A or IIA as described in Claim 1 or 2.

9. (Amended) A method of treating retinal detachment in a mammal by administering an effective retinal detachment treatment amount of a compound of Formula IIIA or IIA as described in Claim 1 or 2.

REMARKS

The Amendment

At page 11, the incorrect chemical structure is amended to a correct structure. Support for the amendment can be found in the parent application 09/101,395, at page 10, lines 10-12. This appears to be an obvious error resulting from improper cut-and-paste.

Other amendments in the specification merely correct typographical errors.

Claim 1 is amended in the description of R_4, R_5 and R_7. R_4 is amended to change "oxo" to hydroxy. Support for the amendment can be found at page 13, line 9. R_5 is amended to delete benzoyl. R_6 is amended to consolidate and simplify the description.

Claims 5-9 are amended to correct the Formula numbers as recited in Claims 1 and 2.

No new matter is added in the amendment. The Examiner is respectfully requested to enter the amendment.

Telephone Interview with Examiner

Applicants thank Examiner Owens for the telephone interview dated January 16, 2003. During the interview, it was agreed that Applicants would provide support for "R_6"and "R_5 and R_6"taken together in Claim 1. It was also agreed that Applicants would submit appropriate

Terminal Disclaimers. It was further agreed that Applicants would provide explanation of the provisos in Claims 1 and 2 to accelerate the prosecution.

Terminal Disclaimers

Applicants are submitting herewith two Terminal Disclaimers over two prior U.S. Patent Nos. 6,348,589 and 5,837,861.

Support for Claim 1

The Examiner has asked Applicants to point out the support for (a) the description of R_6 regarding "where the alkyl groups is optionally linked to form a heterocycle or link to N^3 to form a substituted ring," and (b) the description of "R_5 and R_6 taken together form a 5-membered fused imidazole ring between positions 3 and 4 of the pyrimidine ring, which is optionally substituted on the 4- or 5- positions of the etheno moiety with C_{1-4}alkyl, phenyl, or phenyloxy, which themselves are optionally substituted." Applicants respectfully submit that the exact language can be found at page 13, lines 15-19, in the description of Formula III.

Exclusion of Known Compounds

Applicants are providing the following explanations for the compounds excluded in Claims 1 and 2 as follows for the Examiner to review:

Claim 1

provided that when B = adenine, adenine 1-oxide, or $1,N^6$-ethenoadenine, then:

(a) $R_6 \neq$ oxo when R_4 = oxo, Y = Z = OH and $R_5 = R_7 = R_8$ = H; (elimination of Up_nA, Up_nAO, Up_neA)

(b) $R_7 \neq$ Br when $R_4 = R_6$ = oxo, Y = Z = OH, and $R_5 = R_8$ = H; (elimination of 5-$BrUp_nA$, 5-$BrUp_nAO$, 5-$BrUp_neA$)

provided that when B = adenine, then:

(a) $R_6 \neq$ amino when R_4 = oxo, Y = Z = OH, R_5 is absent, $R_7 = R_8$ = H, and n + m = 0, 1,or 2; (elimination of $Cp_{2,3,4}A$)

(b) $R_7 \neq CH_3$ when $R_4 = R_6$ = oxo, Y = H, Z = OH, and $R_5 = R_8$ = H; (elimination of Tp_nA)

(c) $R_7 \neq$ F when $R_4 = R_6$ = oxo, Y = H, Z = OH, $R_5 = R_8$ = H and n + m = 2; (elimination of (d-5-FU)p_4A)

provided that when B= thymine, Y'=H and Z'= N_3; then $R_7 \neq$ F, when $R_4 = R_6$ = oxo, Y = OH, Z = OH, $R_5 = R_8$ = H, and n+m=0; (elimination of AZTp_2(5-FU)

provided that when B= thymine, Y'=H and Z'= N_3; then $R_7 \neq CH_3$ when $R_4 = R_6$ = oxo, Y = H, Z = N_3, $R_5 = R_8$ = H, and n+m=0; (elimination of AZTp_2AZT)

provided that when B = guanine, then:

(a) $R_6 \neq$ oxo when R_4 = oxo, Y = Z = OH, $R_5 = R_7 = R_8$ = H and n + m =1 or 2; (elimination of Gp_3U, Gp_4U)

(b) $R_6 \neq$ amino when R_4 = oxo, Y = Z = OH, R_5 is absent, $R_7 = R_8$ = H, n + m =1 or 2; (elimination of Gp_3C, Gp_4C)

provided that when B is uridine, or 5-Br-uridine, then

(a) $R_6 \neq$ oxo when R_4 = oxo, Y = Z = OH and $R_6 = R_7 = R_8$ = H; (elimination of Up_nU)

(b) $R_7 \neq$ Br when $R_4 = R_6$ = oxo, Y = Z = OH, and $R_5 = R_8$ = H; (elimination of 5-BrUp_n5-BrU)

provided that when B is 5-FU, then $R_7 \neq$ F, when $R_4 = R_6$ = oxo, Y = H, Z = OH, $R_5 = R_8$ = H, and n + m = 0; (elimination of (5-FU)p_2(5-FU)

provided that when B is cytosine, then $R_6 \neq$ amino, when R_4 = oxo, Y = Z = OH, R_5 is absent, $R_7 = R_8$ = H, and n + m = 1, or 2; (elimination Cp_3C, and Cp_4C)

provided that when B is cytosine, then $R_6 \neq$ oxo, when R_4 = oxo, Y = Z = OH and $R_6 = R_7 = R_8$ = H, and n + m =2 (elimination of Cp_4U).

Claim 2

provided that $R_1 \neq$ H, when X is oxygen, methylene, or difluoromethylene, Y is OH, B is adenine, R_2 is absent, and R_3 is hydrogen; (elimination of Ap_nA)

provided that $R_1 \neq$ H, when n + m = 2, X is oxygen, Y is OH, B is adenine, R_2 is absent, and R_3 is bromo, or 6-aminohexyl; (elimination of 8-BrP_4A, ahaAP_4A)

provided that $R_1 \neq$ H, when n + m = 2, X is oxygen, Y is H, B is adenine, R_2 is absent, and R_3 is H; (elimination of AP_4dA and dAP_4dA)

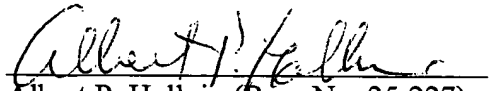
provided that $R_2 \neq$ O, when n + m = 2, X is oxygen, Y is OH, $R_1 = R_3$ = H, and B is adenine, adenine 1-oxide, or $1,N^6$-ethenoadenine; (elimination of AOP_4A, AOP_4AO and AOP_4eA)

provided that R_1 and R_2 do not form a 5-membered fused imidazole ring, when n + m = 2, X is oxygen, Y is OH, R_3 is H, and B is adenine, adenine 1-oxide, or ethenoadenine (elimination of AP_4eA, AOP_4eA, eAP_4eA).

Applicants believe that the above provisos exclude known compounds and provide novelty for the claims.

Respectfully submitted,

Date: January 24, 2003



Albert P. Halluin (Reg. No. 25,227)
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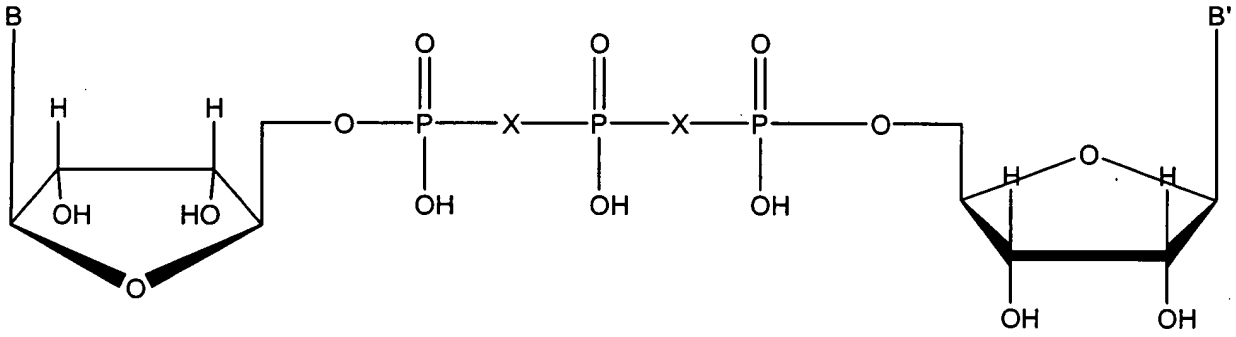
(650) 463-8109

MARKED-UP VERSION SHOWING CHANGES MADE TO SPECIFICATION

At page 11, line 5, and ending at page 11, line 7, delete Formula IB as follows:

"

Formula IB



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and insert --

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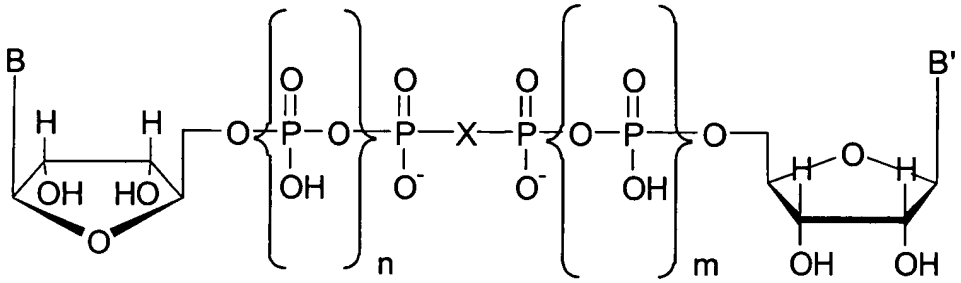


--.

Paragraph starting at page 12, line 15:

Thus the substituted derivatives of adenine include adenine 1-oxide; 1,N^6-(4- or 5-substituted etheno) adenine; 6-substituted adenine; or 8-substituted aminoadenine, where R' of [wherein] the 6- or 8-HNR' groups are chosen from among: arylalkyl (C_{1-6}) groups with the aryl moiety optionally functionalized as described below; alkyl; and alkyl groups with functional groups therein, such as: ([6-aminohexyl]carbamoylmethyl)-, and ω-acylated-amino(hydroxy, thiol and carboxy)alkyl(C_{2-10})- and their ω-acylated-amino (hydroxy, thiol and carboxy) derivatives where the acyl group is chosen from among, but not limited to, acetyl, trifluoroacetyl, benzoyl, substituted-benzoyl, etc., or the carboxylic moiety is present as its ester or amide derivative, for example, the ethyl or methyl ester or its methyl, ethyl or benzamido derivative. The ω-amino(hydroxy, thiol) moiety may be alkylated with a C_{1-4} alkyl group.

Paragraph starting at page 14, line 22:

The compounds of the present invention encompass their pharmaceutically acceptable esters, such as, but not limited to, acetyl and benzoyl esters. The esters may be made by reaction of the desired hydroxy compound with the appropriate acid, activated with carbonyldiimidazole, dicyclohexylcarbodiimide or other suitable condensing agent, or with an acid anhydride or acid chloride with or without a basic catalyst such as a tertary amine, quaternary [amonium] ammonium salt or an inorganic base.

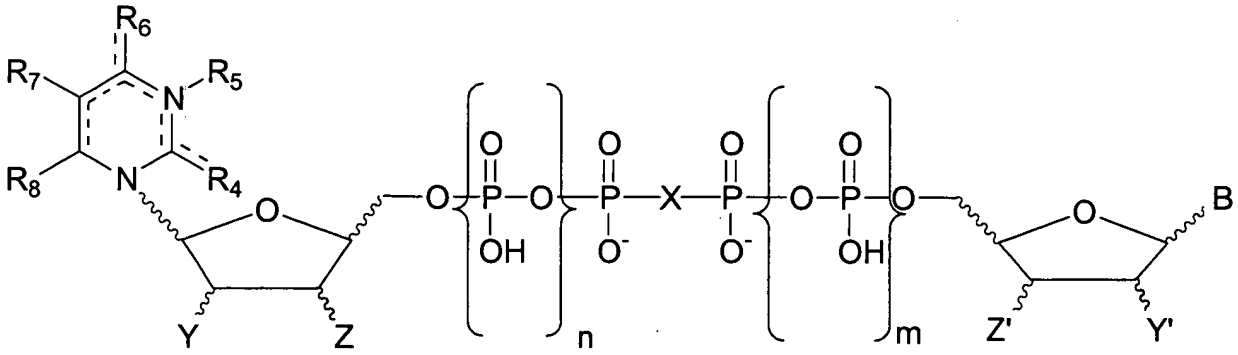
Paragraph starting at page 17, line 1:

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example: sodium carboxymethylcellulose, methylcellulose and sodium alginate. Dispersing or wetting agents may be a naturally-occurring phosphatide or condensation products of an allylene oxide with fatty acids, or condensation products of ethylene oxide with long chain aliphatic alcohols, or condensation products of ethylene oxide with partial esters from fatty acids and a hexitol, or condensation products of ethylene oxide with partial

esters derived from fatty acids and hexitol [anydrides] anhydrides. Those skilled in the art will recognize the many specific excipients and wetting agents encompassed by the general description above. The aqueous suspensions may also contain one or more preservatives, for example, ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

MARKED-UP VERSION SHOWING CHANGES MADE TO CLAIMS

1. (Amended) A compound of Formula IIIA:



Formula IIIA

wherein:

X is oxygen, methylene, difluoromethylene, imido;

n = 0, 1, or 2;

m = 0, 1, or 2;

n + m= 0, 1, 2, 3, or 4;

B is a purine or a pyrimidine residue linked through the 9- or 1-position, respectively;

Z = OH or N_3;

Z' = OH or N_3;

Y = H or OH;

Y' = H or OH;

provided that when Z is N_3, Y is H or when Z' is N_3, Y' is H;

R_4 is [oxo] hydroxy, amino, cyano, aralkoxy, C_{1-6} alkoxy, C_{1-6} alkylamino, or dialkylamino;

R_5 is hydrogen, acyl [or benzoyl], C_{1-6} alkyl, phenyloxy, C_{1-5} alkanoyl or absent;

R_6 is oxo, hydroxy, mercapto, C_{1-4}alkoxy, C_{7-12}arylalkoxy, C_{1-6}alkylthio, amino, C_{1-5} disubstituted amino, triazolyl, C_{1-6}alkylamino or di-C_{1-4}alkylamino, where the alkyl groups is optionally linked to form a heterocycle or link to N^3 to form a substituted ring; or

R_5 and R_6 taken together form a 5-membered fused imidazole ring between positions 3 and 4 of the pyrimidine ring, which is optionally substituted on the 4- or 5-positions of the etheno moiety with C_{1-4}alkyl, phenyl, or phenyloxy, which themselves are optionally substituted;

R_7 is hydrogen, hydroxy, cyano, nitro, substituted and unsubstituted C_{2-8}alkenyl, [C_{1-4}alkyl,] phenyl, substituted and unsubstituted C_{2-8}alkynyl, halogen, [C_{1-4}alkyl, substituted C_{1-4}alkyl,] CF_3, substituted and unsubstituted C_{1-6} [C_{2-6}]alkyl, [C_{2-3} alkenyl,] allylamino, [bromvinyl] bromovinyl, ethyl propenoate, propenoic acid[, C_{2-3} alkynyl, substituted C_{2-3}alkynyl]; or

R_6 and R_7 taken together form a 5 or 6-membered saturated or unsaturated ring bonded through N or O at R_6, such ring optionally contain substituents that themselves contain functionalities;

R_8 is hydrogen, amino or di-C_{1-4}alkylamino, C_{1-4}alkoxy, C_{7-12}arylalkoxy, C_{1-4}alkylthio, C_{7-12}arylalkylthio,carboxamidomethyl, carboxymethyl, methoxy, methylthio, phenoxy or phenylthio; provided that when R_8 is amino or substituted amino, R_7 is hydrogen;

provided that when B = adenine, adenine 1-oxide, or $1,N^6$-ethenoadenine, then:

(a) $R_6 \neq$ oxo when R_4 = oxo, Y = Z = OH and $R_5 = R_7 = R_8$ = H;

(b) $R_7 \neq$ Br when $R_4 = R_6$ = oxo, Y = Z = OH, and $R_5 = R_8$ = H;

provided that when B = adenine, then:

(a) $R_6 \neq$ amino when R_4 = oxo, Y = Z = OH, R_5 is absent, $R_7 = R_8$ = H, and n + m = 0, 1, or 2;

(b) $R_7 \neq CH_3$ when $R_4 = R_6$ = oxo, Y = H, Z = OH, and $R_5 = R_8$ = H;

(c) $R_7 \neq$ F when $R_4 = R_6$ = oxo, Y = H, Z = OH, $R_5 = R_8$ = H and n + m = 2;

provided that when B = thymine, Y'= H and Z' = N_3; then $R_7 \neq F$, when $R_4 = R_6$ = oxo, Y = OH, Z = OH, $R_5 = R_8 = H$, and n + m =0;

provided that when B = thymine, Y' = H and Z' = N_3; then $R_7 \neq CH_3$ when $R_4 = R_6$ = oxo, Y = H, Z = N_3, $R_5 = R_8 = H$, and n + m =0;

provided that when B = guanine, then:

(a) $R_6 \neq$ oxo when R_4 = oxo, Y = Z = OH, $R_5 = R_7 = R_8 = H$ and n + m =1 or 2;

(b) $R_6 \neq$ amino when R_4 = oxo, Y = Z = OH, R_5 is absent, $R_7 = R_8 = H$, n+m=1 or 2;

provided that when B is uridine, or 5-Br-uridine, then

(a) $R_6 \neq$ oxo when R_4 = oxo, Y = Z = OH and $R_6 = R_7 = R_8 = H$;

(b) $R_7 \neq$ Br when $R_4 = R_6$ = oxo, Y = Z = OH, and $R_5 = R_8 = H$;

provided that when B is 5-FU, then $R_7 \neq F$, when $R_4 = R_6$ = oxo, Y = H, Z = OH, $R_5 = R_8 = H$, and n + m= 0;

provided that when B is cytosine, then $R_6 \neq$ amino, when R_4 = oxo, Y = Z = OH, R_5 is absent, $R_7 = R_8 = H$, and n + m = 1, or 2; and

provided that when B is cytosine, then $R_6 \neq$ oxo, when R_4 = oxo, Y = Z = OH and $R_6 = R_7 = R_8 = H$, and n + m =2.

5. (Amended) A pharmaceutical composition comprising a compound of Formula [IA or IB] <u>IIIA or IIA</u> as described in Claim 1 or 2, or a pharmaceutically acceptable salt [therof] <u>thereof</u> together with a pharmaceutically acceptable carrier therefor.

6. (Amended) A method of treating chronic obstructive pulmonary diseases in a mammal by administering an effective chronic obstructive pulmonary disease treatment amount of a compound of Formula [IA or IB] IIIA or IIA as described in Claim 1 or 2.

7. (Amended) A method of treating sinusitis, otitis media or nasolacrimal duct obstruction in a mammal by administering an effective mucus secretion clearing amount of a compound of Formula [IA or IB] IIIA or IIA as described in Claim 1 or 2.

8. (Amended) A method of treating dry eye in a mammal by administering an effective dry eye treatment amount of a compound of Formula [IA or IB] III A or IIA as described in Claim 1 or 2.

9. (Amended) A method of treating retinal detachment in a mammal by administering an effective retinal detachment treatment amount of a compound of Formula [I] IIIA or IIA as described in Claim 1 or 2.

PTO/SB/26 (10-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT	Docket Number (Optional) 03678.0022.CNUS02

In re Application of: William Pendergast, et al.

Application No.: 10/007,451

Filed: November 6, 2001

For: Certain Dinucleotides and Their Use as Modulators of Mucociliary Clearance and Ciliary Beat Frequency

The owner*, Inspire Pharmaceuticals, Inc., of 100% percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. 6,348,589. The owner hereby agrees that any patent so granted on the instant application shall be enforceabe only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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2. ☒ The undersigned is an attorney or agent of record.

Signature 1/24/03 Date

Albert P. Halluin(Reg. 25,227)/Viola Kung (Reg. 41,131)
Typed or printed name

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